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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
LUM, LEON YUN BON	

ART UNIT	PAPER NUMBER
1641	

DATE MAILED: 06/21/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/595,720	CHERONIS ET AL.	
	Examiner	Art Unit	
	Leon Y Lum	1641	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *24 November 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-34 and 45* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-34 and 45* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *04 October 2002* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Allowable Subject Matter

1. The indicated allowability as conveyed by the previous Examiner to the Attorney of Record on March 24, 2004 of claims 1-34 and 45 is withdrawn in view of the newly discovered reference(s) to Chandler et al (USP 4,769,216), Snitman et al (USP 5,273,882), Nishimura et al (USP 5,583,005), Griffin et al (USP 5,756,291), Li (USP 6,180,348 B1), Bieche et al (International Journal of Cancer, 78:661-666, 1998), Huang et al (Analytical Biochemistry 237:115-122, 1996), Male et al (Advanced Immunology, 1987), and Mandal et al (Bioconjugate Chemistry 8:798-812, 1997). Rejections based on the newly cited reference(s) follow.

Specification

2. The disclosure is objected to because of the following informalities: the reference numbers 103 and 104 referring to items X and Y, respectively, on page 21, line 4 seem to be incorrect in light of Fig. 1. It seems as if X and Y should be referred to as 102 and 103, respectively.

Appropriate correction is required.

Claim Objections

3. Claims 1 and 45 are objected to because of the following informalities: the word "the" should be inserted after "with" and before "aptamer" on line 6 of the claim 1 and lines 6-7 of claim 45. Appropriate correction is required.

4. Claim 29 is objected to because of the following informalities: the word "and" should be inserted after "aliquots," and before "a first" on line 2 of the claim. Appropriate correction is required.

Claim Rejections - 35 USC § 112

5. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

6. Claims 1-34 and 45 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

7. In claim 2, line 2, the phrase "natural or synthetic" is vague and indefinite. It is not clear whether the phrase applies to just the "single-stranded DNA" (line 2) or all of the limitations following the phrase. Applicant is advised to clarify the claim.

Claim Rejections - 35 USC § 103

8. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

9. The factual inquiries set forth in *Graham* v. *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

10. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

11. Claims 1-2, 6-9, 13-14, 16-18, 20-24, 33, and 45 are rejected under 35 U.S.C. 103(a) as being unpatentable over Li (USP 6,180,348 B1) in view of Bieche et al (International Journal of Cancer, 78:661-666, 1998).

In the instant claims, Li reference teaches a method of admixing (adding to the first sample) a collection of oligonucleotides on solid supports having different nucleotide sequences (preparation of a nucleic acid aptamer specific for each target molecule) with magnetic beads covered with target molecules (one or more target molecules in a first sample) under conditions suitable for the binding of oligonucleotide to the target molecule (allowing substantially all of the target molecules in the first sample of bind with the aptamers) and applying magnetic force to isolate one or more solid supports attached with magnetic beads (separating unbound aptamers from the first sample and recovering a second sample containing the aptamer bound to target molecules) (column 2, lines 6-38). In addition, Li also teaches that oligonucleotides are synthesized on solid supports of PEG-grafted polystyrene beads (immobilized ligands wherein the ligands bind to the unbound aptamers) (column 10, lines 38-50) wherein the PEG linkers are the ligands, the isolated oligonucleotides can be amplified with polymerase chain reactions (PCR) (using replicative procedure) (column 7, line s 49-51), and that the oligonucleotides isolated can be used to detect and quantitate target molecules (related to the concentration of target molecules in the first sample) (column 7, lines 56-61).

However, Li reference does not teach that the replicative procedure is quantitative and that measuring the amount of aptamer includes denaturing the

aptamer, adding oligonucleotide primers, and determining a number of replicative cycles.

Bieche et al reference teaches a real-time quantitative PCR detection method in order to provide a rapid, sensitive, and accurate method of analyzing samples (page 666, 2nd column, 3rd paragraph), present quantitative analysis of DNA, and to detect samples with minimal starting quantities (page 661, 2nd column, 2nd paragraph). Bieche et al reference also teaches that C_t, the threshold cycle number (replicative cycles), determines the target copy number (amount of aptamer) (page 662, 1st column, 5th paragraph), oligonucleotide primers are added (page 662, 2nd column, 3rd and 9th paragraph), and amplification occurs (denaturing the aptamer) (page 662, 2nd column, 9th paragraph) in order to perform real-time quantitative PCR.

Therefore, it would have been obvious to one of ordinary skill in the art at the time of the invention to include in the method of Li, the method of quantitative PCR, as taught by Bieche et al, in order to provide a rapid, sensitive, and accurate method of analyzing samples, present quantitative analysis of DNA, and to detect samples with minimal starting quantities. One of ordinary skill in the art would have reasonable expectation of success in applying the method of quantitative PCR, as taught by Bieche et al, in the method of Li, since Li teaches the application of regular PCR to amplify DNA and quantitative PCR is simply a modification of regular PCR to produce numerical results.

It would also have been obvious to one of ordinary skill in the art at the time of the invention to include in the method of Li, the steps of determining C_t, the threshold

cycle number, to obtain amount of target, adding oligonucleotide primers, and amplification to denature the aptamer), as taught by Bieche et al, in order to perform real-time quantitative PCR since the steps taught are essential to the process of real-time quantitative PCR.

With respect to claims 6-9, 13-14, and 16-17, Li reference additionally teaches that target molecules are antibodies, proteins, drugs, toxins and growth hormone (column 2, lines 54-67).

12. Claims 3-4 are rejected under 35 U.S.C. 103(a) as being unpatentable over Li (USP 6,180,348 B1) in view of Bieche et al (International Journal of Cancer, 78:661-666, 1998), and in further view of Griffin et al (USP 5,756,291).

Li and Bieche et al references have been disclosed above, but fail to teach that target molecules are present in a sample at molar concentrations less than, equal to, or greater than their dissociation constants with respect to aptamers.

Griffin et al reference teaches binding of aptamers to Factor X and ICAM-1, which have molar concentrations of 1M and 10M, respectively (column 100, line 64 and column 125, line 22). Griffin et al reference also teaches that the binding affinities of the target to oligonucleotide aptamers may range from 100M to 1M and that the smaller the values of Kd are advantageous in order to obtain more initial binding of the target to oligonucleotides (column 21, lines 16-25). Griffin et al also teach aptamers with a binding region capable of specific binding to a molecule with a dissociation constant

(Kd) of less than 20 nM in order to bind target molecules that do not normally bind to oligonucleotides at that specific Kd (column 42, lines 39-44).

Therefore, it would have been obvious to one of ordinary skill in the art at the time of the invention to include in the methods of Li and Bieche et al, target molecules of Factor X and ICAM-1, which have molar concentrations less than, equal to, or greater than the dissociation constant Kd, depending on oligonucleotide aptamers, as taught by Griffin et al, in order to obtain specific and initial binding between targets of different concentrations and aptamers chosen specifically for the targets, One of ordinary skill in the art would have reasonable expectation of success in choosing target molecules of Factor X and ICAM-1, as taught by Griffin et al, in the methods of Li and Bieche et al since Li and Bieche et al teach the amplification of oligonucleotides, including oligonucleotides at low concentrations, and Factor X and ICAM-1 can be detected by aptamer amplication using the same methods.

13. Claims 5 and 15 are rejected under 35 U.S.C. 103(a) as being unpatentable over Li (USP 6,180,348 B1) in view of Bieche et al (International Journal of Cancer, 78:661-666, 1998), and in further view of Tabor et al (USP 5,534,407).

Li and Bieche et al references have been disclosed above. Li reference additionally teaches that the target molecule is any molecule capable of forming a complex with an oligonucleotide, including nucleic acids (column 2, lines 54-59). However, Li and Bieche et al fail to disclose that the target molecules are low abundance molecules and the sample is urine.

Tabor et al reference teaches that testing on urine can be performed with samples of low nucleic acid concentrations using the genetic amplification method of PCR in order to test for the presence of low concentrations of a virus or bacteria (column 8, lines 43-52).

Therefore, it would have been obvious to one of ordinary skill in the art at the time of the invention to include in the methods of Li and Bieche et al, the testing of low nucleic acid concentrations from urine samples using PCR, as taught by Tabor et al, in order to test for low concentrations of a virus or bacteria. One of ordinary skill in the art would have reasonable expectation of success in testing for low nucleic acids concentrations in blood, as taught by Tabor et al, in the methods of Li and Bieche et al, since Li and Bieche et al teach testing for nucleic acids using PCR, and Tabor et al use the same method to detect low abundance molecules.

14. Claims 10-12 are rejected under 35 U.S.C. 103(a) as being unpatentable over Li (USP 6,180,348 B1) in view of Bieche et al (International Journal of Cancer, 78:661-666, 1998), and in further view of Mandal et al (Bioconjugate Chemistry 8:798-812, 1997).

Li and Bieche et al references have been disclosed above, but fail to disclose that target molecules are metal complexes.

Mandal et al reference teaches the interactions of transition metal complexes with DNA in order to aid in the design of drugs (page 798, 1st column).

Therefore, it would have been obvious to one of ordinary skill in the art at the time of the invention to include in the methods of Li and Bieche et al, target molecules that are metal complexes, as taught by Mandal et al, in order to produce DNA-metal complexes to aid in the design of drugs. One of ordinary skill in the art would have reasonable expectation of success in using metal complexes, as taught by Mandal et al, as targets in the method of Li and Bieche et al, since Li and Bieche et al teach that target molecules can be any molecule that binds to oligonucleotides, and the metal complexes taught by Mandal et al are capable of binding to DNA.

15. Claim 19 is rejected under 35 U.S.C. 103(a) as being unpatentable Li (USP 6,180,348 B1) in view of Bieche et al (International Journal of Cancer, 78:661-666, 1998), and in further view of Snitman et al (USP 5,273,882) and Huang et al (Analytical Biochemistry 237:115-122, 1996).

Li and Bieche et al references have been disclosed above, but fail to disclose that the immobilized ligand is immobilized on an affinity column.

Huang et al reference teaches the binding of biotinylated DNA to streptavidin-coated polystyrene (page 115, 1st column and page 122, 1st column) and Snitman et al reference teaches the binding of biotin-conjugated DNA to a streptavidin-sepharose affinity column (column 2, lines 26-29) in order to perform DNA hybridization assays to isolate and identify target DNA sequences.

Therefore, it would have been obvious to include in the methods of Li and Bieche et al, immobilizing biotin-streptavidin ligand complexes to an affinity column, as taught

by Huang et al and Snitman et al, in order to perform DNA hybridization to isolate and identify DNA sequences. One of ordinary skill in the art would have reasonable expectation of success in immobilizing biotin-streptavidin complexes as ligands to an affinity column, as taught by Huang et al and Snitman et al, in the methods of Li and Bieche et al, since Li and Bieche et al teach that DNA aptamers can bind to nucleic acid targets (hybridization) in assays where the aptamers also bind to polystyrene solid supports through linkers, and Huang et al teach that biotin-streptavidin ligands can be used as linkers on polystyrene surfaces and Snitman et al teach that biotin-streptavidin ligands can be immobilized on affinity columns for the purposes of DNA hybridization assays.

16. Claims 25-28 are rejected under 35 U.S.C. 103(a) as being unpatentable over Li (USP 6,180,348 B1) in view of Bieche et al (International Journal of Cancer, 78:661-666, 1998), and in further view of Male et al (Advanced Immunology, 1987) and Nishimura et al (USP 5,583,005).

Li and Bieche et al references have been disclosed above, but fail to teach that the target molecules include IgE, a plurality of antibody molecules belonging to different subclasses characterized by different hypervariable regions, that the target molecules are a subclass of an antibody having a characteristic hypervariable region, that the aptamer binds to a constant region of the antibody, and that the immobilized ligand is the constant region of the antibody for removing unbound aptamer.

Male et al teach antibodies divided into the classes of IgG, IgM, IgA, IgD, and IgE, which differ in their Fc regions in order to interact with a diversity of antigens (page 2.1, 1st column). Nishimura et al teach IgE with different regions in order to bind specific monoclonal antibodies for IgE (column 1, lines 52-57).

Therefore, it would have been obvious to include in the methods of Li and Bieche et al, target molecules including immunoglobulins with different Fc regions and IgE with different binding regions, as taught by Male et al and Nishimura et al, in order to interact with a diversity of antigens and bind specific monoclonal antibodies for IgE. One of ordinary skill in the art would have reasonable success in applying immunoglobulins and IgE with different hypervariable regions, as taught by Male et al and Nishimura et al, in the methods of Li and Bieche et al, since Li and Bieche et al teach that target molecules can be any molecule that can bind to oligonucleotide aptamers, including antibodies, and immunoglobulins including IgE are one type of antibody.

It would also be obvious to one of ordinary skill in the art at the time of the invention that the aptamer would bind to a constant region of the antibody since antibodies inherently have a specific binding region to an antigen (Male et al, page 2.1, 1st column, 2nd paragraph) and that the immobilized ligand is the constant region of the antibody since Male et al and Nishimura et al teach that antibodies can be used as ligands in affinity columns for removing unbound aptamers.

17. Claims 29-32 and 34 are rejected under 35 U.S.C. 103(a) as being unpatentable over Li (USP 6,180,348 B1) in view of Bieche et al (International Journal of Cancer,

78:661-666, 1998) and Nishimura et al (USP 5,583,005), and in further view of Chandler et al (USP 4,769,216).

Li, Bieche et al, and Nishimura et al references have been disclosed above and Li additionally teaches that aptamers can be used to separate and purify target molecules (column 7, lines 56-61), but fail to disclose that the second sample is divided into a plurality of aliquots and that the aliquots are contacted with immobilized ligands to separate antibodies with different hypervariable regions, and that aptamers in recovered samples are assayed using the quantitative replicative technique.

Chandler et al teaches a method wherein a sample is passed simultaneously through multiple capillaries or tubes with antigens attached to the interior of the capillaries or tubes, in order to detect or determine the presence of antibodies in the sample (column 2, lines 5-14).

Therefore, it would have been obvious to one of ordinary skill in the art at the time of the invention to include in the methods of Li, Bieche et al, and Nishimura et al, passing a sample through multiple compartments with immobilized antigens, as taught by Chandler et al, in order to determine the presence of antibodies in the sample. One of ordinary skill in the art would have reasonable expectation of success in passing the sample through multiple capillaries or tubes, as taught by Chandler et al, in the method of Li, Bieche et al, and Nishimura et al, since Li, Bieche et al, and Nishimura et al teach the separation of target molecules, and that the target molecules are antibodies, which inherently bind to specific antigens and would attach to the antigens immobilized on the capillaries and tubes. The method of aptamer binding to target molecules, as taught by

Li, Bieche et al, and Nishimura et al is also analogous to the passing of fluid, as taught by Chandler et al, wherein a difference lies in a single step of binding versus simultaneous, multiple binding. However, it would have been obvious to one of ordinary skill in the art at the time of the invention to perform simultaneous, multiple binding, as taught by Chandler et al, after obtaining the second sample, as taught by Li, Bieche et al, and Nishimura et al, in order to obtain specific antibody-antigen binding and to separate aptamers that may bind to specific and different regions of the antibody IgE into a third sample. It would also have been obvious to one of ordinary skill in the art to perform quantitative PCR on aptamers in the third sample after the antibody-antigen binding in the multiple capillaries or tubes since oligonucleotide amplification would be the same method used in the step to amplify the second sample that has been taught by Li, Bieche et al, and Nishimura et al.

Conclusion

18. The prior art made of record and not relied upon is considered pertinent to applicant's disclosure.

Toole et al (USP 5,582,981) teach oligonucleotide aptamers selected to bind target biomolecules and application of PCR to amplify the aptamers.

Jayasena et al (USP 5,989,823) teach nucleic acid aptamer binding on solid supports to a target molecule, including non-nucleic acid targets.

Terstappen et al (USP 5,646,001) teach the separation of distinct subpopulations of biological entities through affinity binding with antibodies.

Gold et al (USP 6,242,246 B1) teach nucleic acid ligands on biochips that bind to target molecules including proteins, hormones, sugars, metabolic byproducts, drugs, and toxins.

Berndt et al (Analytical Biochemistry 225:252:257, 1995) teach quantitative PCR using DNA hybridization assays.

Desjardin et al (Journal of Clinical Microbiology, July:1964-1968, 1998) teach quantitative PCR analysis through comparisons between two quantification methods.

Gibson et al (Genome Research, 6 :995-1001, 1996) teach real-time quantitative RT-PCR methods to quantitate small amounts of DNA.

Gold, Larry (The Journal of Biological Chemistry, 270(23):13581-13584, 1995) teaches oligonucleotides in specific binding to target molecules for diagnostic assays.

Greenspan et al (FASEB J, 7:437-444, 1993) teach idiotypes and structural diversity of immunoglobulins.

19. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Leon Y Lum whose telephone number is (571) 272-2878. The examiner can normally be reached on 8:00am-5:00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Long Le can be reached on (571) 272-0823. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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